An additional evidence of lowered body resistance in these animals was incidentally apparent during the experiments on sugar tolerance about to be described. This procedure makes all of the animals sick, and a high proportion of hypophysectomized animals succumb. Thus, in our series to date, thirty-two tests on seventeen hypophysectomized animals resulted in death for eleven, whereas in fourteen tests on five normal animals, death came to but one. This is a difference of one death for every three tests in the hypophysectomized animals, and one for every fourteen in the controls.

Plans for studies in other phases of immunity than that detailed above were made, but had to be abandoned because of lack of funds for the rather costly work in developing immunity.

SUGAR TOLERANCE CURVES

The sugar curves presented here were obtained from seventeen hypophysectomized animals. Five normal animals were used as controls. The results indicate a change in reaction, depending upon the lapse of time following operation. Thus at two and three weeks there is a distinct increase in the ability of the body to utilize sugar, while at five weeks and upward the reverse is true, the inability becoming progressive.

These changes would seem to indicate that insulin was more readily available two to three weeks after operation than in normal animals, but that at the end of five weeks and onward insulin could not be made available in sufficient quantities to hold the blood sugar even near the normal curve. The charts presented are average curves of groups sufficiently large to be significant. Only rarely did an individual animal deviate from the general trend of the group.

Chart 3 presents average curves of eight animals five weeks after removal of the gland, twelve animals from two to three weeks after operation, and a control curve of nine tests on five normal animals.

Chart 4 gives as an illustration the difference in reaction of two animals at two and five weeks after hypophysectomy, indicating that the changes may be very extreme during this span of time.

One other item of significance is that the fasting sugar level in the hypophysectomized animals is, with but few exceptions, considerably below the lowest figures for the control animals. This would suggest, as a possible explanation, glycogen depletion of liver and muscles.

Most animals that succumb during this test do so within six hours after the introduction of glucose into the fasting stomach. They become "dopy," breathe slowly, lose the ability to walk, and die gradually. A very high blood sugar is found at death. Death occurs in so short a time as to make acidosis at best an awkward explanation, particularly because of the abundance of sugar available, though they seem to have many of the symptoms of coma. It seems as though the presence of a high blood sugar is in itself deleterious. It is certain that some increase in blood viscosity occurs, for in these animals, as occasionally in others, it became impossible to obtain blood from the tail no matter how short it was severed.

CONCLUSIONS

1. Water intake is persistently increased in hypophysectomized animals. This ranged from eight times the normal, following operation, to 2.5 times the normal five and eight weeks following operation in the group reported, and probably continues. Food intake in this series was not significantly altered.

2. A progressive weight loss of approximately .5 gram per day occurred in a group of twenty-eight hypophysectomized animals between the fourth and twenty-first days after operation, and continues at about the same rate.

3. Weight for weight, the biologic potency of the thyroid tissue of hypophysectomized animals is equivalent to that of normal animals, but there is less of it.

4. In several respects hypophysectomized animals show a measurable decrease in the ability of the body to resist insult.

5. An increase in the ability of the hypophysectomized animal to utilize sugar occurs two weeks following removal of the gland, with a reversal at five weeks. From this point the decreased tolerance appears to become progressive.

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LIVING GRAFTS OF ENDOCRINE GLANDS*

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III†

COMMENT ON TWO CLINICAL CASES

WE are fortunate in that recently we have had two clinical cases that offered unusual experimental opportunities—a case of Paget's disease, and one of surgical parathyroid tetany. The case of Paget's disease was operated upon because

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we hoped to find a hypertrophy or an adenoma of the parathyroids. At operation the parathyroids showed no gross pathologic changes, but because of the patient's condition one parathyroid was removed for study and its possible use for grafting. Sections of this gland showed no evidence of pathology. About nine-tenths of the gland was maintained by tissue cultures, some of which were grown on slides in the usual manner and the rest in tiny flasks. For the first two weeks a medium was used which contained the serum of the patient from whom the gland had been removed. The plasmatic medium was prepared in the usual way and also contained the beef embryo juice, which likewise was used in the animal experiments. Growth of the tissue was very rapid and liquefaction was troublesome, making it necessary to change the medium frequently. At this point it was decided to transfer this cultured material into a medium containing the fluids of the patient suffering from parathyroid tetany. Therefore she was bled when necessary and her serum and plasma used for a period of four weeks in the culture media of the growing human parathyroid. The growth of the tissue in this foreign medium was just about as rapid as it had been previously, but there was less liquefaction. The liquefaction fluid produced while the tissue was in the serum of the donor had a pH of 6.9 and was saved and kept in the refrigerator. That produced while it was in the serum of the recipient was saved separately in the same manner, and both fluids, through the courtesy of Doctor Schelling of the Harriet Lane Home, were tested for their content of parathyroid secretion. The method that he used was the effect of these solutions on the calcification of the bones of young rats. These experiments were negative, as might have been expected, had we known of the experiments of W. J. Allerdyce,[5] whose work showed that tissue enzymes destroy parathormone almost as fast as it is formed, especially if allowed to stand in contact with them. At the end of the four-week period on February 17, 1933, the tissue cultures were transplanted into the areolar tissue of the axilla of the patient with tetany. This patient into whom they were transplanted has been suffering with tetany in a latent form for over sixteen months following thyroidectomy without any apparent improvement, and goes into active tetany at the beginning of each menstrual period. At the time that the transplantation was done, her calcium was 6.80 (milligrams per 100 cubic centimeters) and phosphorus was 5.61. She had a positive Trousseau in sixty seconds, and a positive Chvostek. Four days previous to the time of transplantation she had had an attack of active tetany so severe that she was unconscious for nearly half an hour. One week previous to the implantation of the graft her calcium was 6.62 (February 3), but phosphorus was not done. On January 27 her calcium had been 4.94; but in spite of this low calcium she was feeling quite well. The end-results of this experiment will have to be reported later.

PLANS CONCERNING PRESENT AND FUTURE STUDIES

Again repeating that this paper is a preliminary report, we wish to set forth the lines along which our present work is continuing and our future plans are laid. Thus far we have used only two of the ductless glands for grafting experiments—the thyroid and the parathyroid—and with each have had at least a measure of success. It is our purpose to extend this study to include grafting experiments with adrenal cortex, islands of Langerhans, hypophysis, and other endocrine organs. These will be dealt with in the same manner as thyroid and parathyroid. More basically important, we expect to try cross-species grafting by the same technique. In the earlier period of this work we tried various cat-dog grafts, before the development of the tissue culture adaptation to host serum method, with the uniform failure that others have reported. We recognize that because of the promise of our experiments in homografts within the same species, we have no justification to expect similar results in heterografts across species lines, yet it is certainly the next logical step in the extension of the method, and one of the greatest importance. Because it is obvious that if a method of successful cross-species grafting can be developed, the practical utility of its clinical application will be enormously enhanced. Another phase of investigation that has already been planned and started in preliminary fashion is the study of the specific chemical properties of the cells of endocrine glands while growing in cell cultures. It will be interesting certainly, and possibly of value, to know whether cell cultures of thyroid elaborate detectable amounts of thyroxin, for instance, or whether cultures of Langerhans' cells produce insulin *in vitro*. Among other opportunities that this method may offer is a way to test further Halsted's suggested law of deficiency as a requirement for successful endocrine grafts. It is very apparent that if a regularly successful technique of gland grafting is evolved, this suggestion of Doctor Halsted's can be readily submitted to conclusive experiment. There are further and more theoretical problems of general biology that suggest themselves as possible subjects for study by such a method. For instance, can we reproduce experimentally the diseases of glandular excess by grafting masses of tissue into normal animals? Can we study the supposed balance between endocrine glands by this method? We make bare mention of the obvious approach this may offer to the "rejuvenation" idea, so often and so basely exploited before. To the imagination of the clinician, less abstruse but more practical possibilities suggest themselves. As was stated in the beginning of this paper, the treatment of those disorders of the endocrine glands involving excess are dealt with on a principle that may fail in individual cases but that is sound and successful in general. The treatment of the deficiency disorders has made great progress recently, but it is still resting on an essentially unsatisfactory foundation—the administration of externally prepared chemical products. What a boon if we could replace the lacking products, not by repeated introduction from without, but by constant steady elaboration from within the body itself! What a triumph if we could give back to the myxedematous patient a working thyroid, to the diabetic a functioning insulin apparatus, and to all the other sufferers from endocrine insufficiencies the living tissues that would restore them to normal health and function! Surely this is a dream worth cherishing, and an attainment worth working for.

SUMMARY OF PRESENT CONCLUSIONS

But while we naturally and rightly cherish our dreams of future possibilities, we emphasize again that we are not deluded and wish to delude no one else as to the limited extent of our actual present results. It may be well to conclude this paper with a brief summary of our conclusions, and their meagerness will act as a correction to any overenthusiasm that may be inferred from the preceding paragraph.

1. The success of grafts of endocrine glands depends on at least three principal factors, and possibly others not yet known. Those factors are the site at which the graft is placed, the physical form of the grafted tissue, and the chemical adjustment of the graft to the host.

2. As concerns the site of the graft, it should be placed in a location of loose structure, free from pressure, near a good blood supply but not too vascular, and easy of access.

3. As concerns the physical form of the graft, it should be either in finely divided fragments of the original gland, or in the form of tissue cultures grown from the original gland. Such forms of graft permit the individual cells to come in close and quick contact with nutrient substances without depending at first upon the development of an organized blood supply.

4. The chemical adaptation of graft to host may be sought by growing the graft as a tissue culture in a medium made up from fluids of the host's body, thus providing an opportunity for preliminary adjustment of the graft to its future chemical environment.

5. By the observance of these requirements, in a series of experiments thus far not sufficient to be conclusive, a promising measure of success has been attained.

6. The subject as a whole is full of such great possibilities of clinical value and scientific interest that it deserves active and earnest prosecution.

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THE KNEE JOINT—ITS FUNCTIONAL ANATOMY AND THE MECHANISM OF CERTAIN INJURIES*

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ANY consideration of the functional anatomy of the knee joint and of the mechanism of injury, historically, focuses attention on the work of four men. One hundred and fifty years ago William Hey [1] of Leeds recognized clinically and treated successfully the condition known as internal derangement of the knee joint, and was the first medical man to invade this province of the bone setter. To Edinburgh we turn for the work of the other three. There, John Goodsir,[2] the master anatomist, carried out his remarkable work on the mechanism of the knee joint while professor of anatomy during the years 1846-67. To his demonstrator, Thomas Annandale, who succeeded Lister as professor of surgery in Edinburgh, fell the distinction of performing the first operation for a tear of the semilunar cartilage. This operation was performed in 1883, just fifty years ago, and was followed by the experimental work of Annandale's pupil, Scott Lang,[3] who carried out the earliest experiments on the mechanism of production of such internal derangements of the knee joint.

This paper is very largely an expression of personal opinion derived from repeated examinations of the knee joint, in health, in injury, and on the cadaver.

From time to time I have repeated much of the work of others and so I am very largely in agreement with their interpretations except in certain details. It is not possible in such a short discourse to enter into a critical examination of the literature, nevertheless wherever I have cited others I have personally verified and agree with their opinions.

THE KNEE JOINT STRUCTURE AND MOVEMENTS

The knee joint is a double articulation enclosed in a common synovial membrane. Of these two articulations the chief is that which occurs between the femur and the tibia, which also is in itself double. The articulation between patella and femur will not be discussed in this discourse; and in what follows, knee joint refers arbitrarily to the tibiofemoral joint.

The knee joint, classed as a freely movable or diarthrodial joint, conforms to a general principle which is characteristic of most, if not all, such diarthrodial joints. This principle is exhibited in a dual function of the articular surfaces. Diarthrodial joints, and especially those of the lower extremity, must subserve two purposes. As Walmsley,[4] following Goodsir,[2] puts it, the first is the transmission of body weight through a temporarily stabilized couple, the components of which are displaceable; and the second is the free movement of the components on one another by the action of the related muscles. Stabilization of a joint is

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